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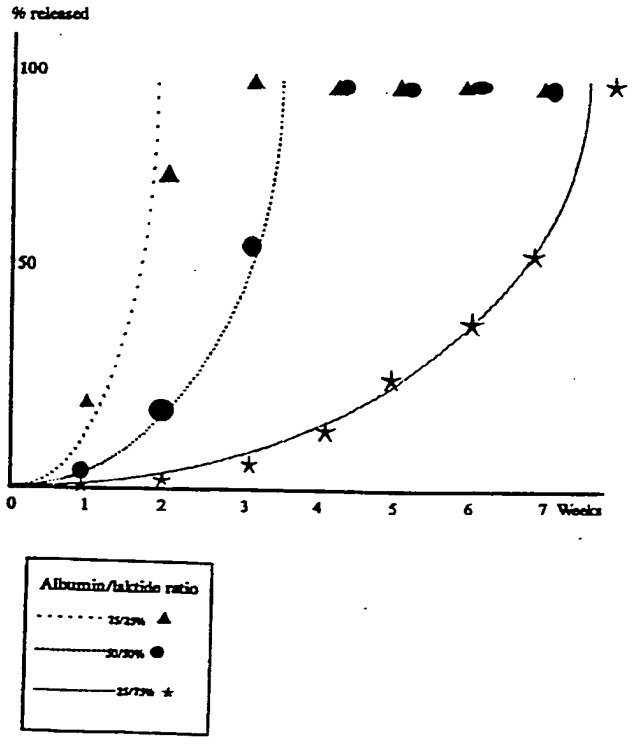
(54) Title: DRUG DELIVERY SYSTEM, METHOD FOR PREPARING THE SAME, AND USE THEREOF

(57) Abstract

This invention relates to a drug delivery system comprising one or more pharmacologically active substances and a polysaccharide matrix having pseudoplastic properties, to a method for preparing the same, and to the use thereof for providing slow release of the active substance(s) in a biocompatible environment following in vivo injection thereof. The method enables combining of the active substances and the matrix without prior suspending or dissolving the former in an aqueous media. The drug delivery system allows injection of aggregated drugs giving prolonged drug release in a biocompatible environment.



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Drug delivery system, method for preparing the same, and use thereof

The present invention relates to a drug delivery system comprising one or more pharmacologically active substances and a polysaccharide matrix having pseudoplastic properties, to a method for preparing the same, and to the use thereof for providing slow release of the drug in a biocompatible environment following in vivo injection.

Parenteral drug administration by injection is readily achieved with water soluble drugs dissolving easily in the diluent, in most cases physiological saline. However, in performing injection of non-soluble drugs the drug particles tend to occlude the hypodermic needle not only making the injection thereof difficult but also causing a loss of the drug and, thereby, an inexactly administred dose. Injection of slowly dissolving drugs requires, in addition the the above drawbacks of the non-soluble drugs, a considerable amount of time for preparing the solution to be injected. Pre-prepared injectable drugs are subject to substantial activity losses and, therefore, it is desired to keep the drug and diluent apart prior to use.

To achieve a slow release or depot action of a drug in vivo it is known to aggregate, for example lactide aggregate, the drug. This aggregate is implanted to a desired position within the human or animal body or injected. An example of this is contraceptive drugs being aggregated and then implanted subcutaneously, for example in the form of a so called contraceptive-rod for prolonged use. These depot preparations are extremely desirable since they give a low dosis uniformly spread throughout the day and night, and are also suitable for individuals with a bad memory and for animals. The known drug aggregates cannot be injected into a desired site of the human or animal body and remain there until the drug delivery is completed. The solution to this problem has hitherto been implantation of larger drug aggregates, such as the above mentioned contraceptive-rod, but these are not biocompatible and, therefore, cause irritation of adjacent tissue and sometimes have to be removed surgically.

The properties of glucoseamine glucans, for example hyaluronic acid and its derivatives, have been known for a long time. The biocompatibility and lack of immunological response in vivo are the main properties rendering these useful agents within the medical field. The most known use of hyaluronic acid is for ophtalmic surgery. Also, a known use thereof is as a carrier for water-soluble drugs, see for example US 804 178.

EP 224 987 describes a combination of a pharmacologically active substance and a pseudoplastic gel being biocompatible and injectable. However, this the active substance is not aggregated and, therefore, the combination does not give a depot or slow release action of the drug in vivo following injection thereof. Furthermore, the methods of preparing the combination involves dissolving or diluting the drugs in aqueous solution which is time consuming and only enables use of water-soluble drugs because water-unsoluble drugs precipitate in the aqueous solution.

US 4 495 471 describes a pseudoplastic gel combination intended for terapeutic percutaneous embolization of, for example, aneurysms, and comprising, in addition to the pseudoplastic gel, thrombin, and optional: metal powder, Ba-salt, low molecular weight drug. It does not contain an aggregated drug and, therefore, a prolonged depot action of the drug is neither intended nor achieved.

An object of the present invention is to enable readily preparation and injection of a drug delivery system comprising a water unsoluble or badly soluble drug and a pseudoplastic gel without the above drawbacks associated with prior art, ie precipitation, clogging, and loss of drug material. Another object of the invention is to provide injectable and biocompatible depot preparations.

These objects are achieved with a drug delivery system comprising one or more pharmacologically active substances and a polysaccharide matrix having pseudoplastic properties, and with

a method of parental injection, according to claims 1 and 12, respectively.

The present invention takes advantage of the pseudoplastic properties of, for example, hyaluronic acid having shearing dependent viscosity. By performning repeated experiments, we surprisingsly found that water unsoluble or slowly soluble, for example particulate, cristalline and freeze dried, drugs not possible to inject in water or physiological saline without the above mentioned drawbacks readily can be prepared and injected in association with pseudoplastic solutions.

According to the method of the invention, one or more water unsoluble or badly soluble drug is first brought together with the pseudoplastic gel vehicle in a vial. Thereafter, the combination is aspirated into a syringe provided with a cannula, the aspirating procedure being repeated, under visual observation, until substantially all of the drug particles are incorporated into the pseudoplastic gel. Now, the combination is ready for injection. For storing purposes, the drug is suitably kept in one vial and the pseudoplastic gel in another vial, preferably a syringe. At the time of use, the gel is pushed out of the syringe into the drug vial and thereafter the combination is drawn back into the syringe, the drug being mixed with the gel substantially during the low viscosity phase of the gel, ie when it passes through the cannula. The method of the invention allows injection of water unsoluble or badly soluble drugs without prior suspending or dissolving thereof in aqueous media. This is not only time saving but also eliminates the problems associated with prior art, ie precipitation, clogging and loss of valuble drug material.

Alternatively, the pseudoplastic gel may be dehydrated initially and rehydrated together with the drug particles prior to use, capturing the drug within the pseudoplastic gel.

In the present invention, there is used a polysaccharide matrix

with pseudoplastic properties as a vehicle of one or more pharmacologically active substances. The pseudoplastic gel comprises water and 0,05 to 20 % w/w matrix and examples thereof include glucoseamine glucans, hydroxy ethylcellulose, carboxy methyl cellulose or xanthan gum. The preferred matrix is glucose amine glucans providing an excellent biocompatibility eliminating irritation of adjacent tissue when administred in vivo.

Examples of drugs which may be used in association with the invention, are hormones, growth factors, enzymes, antibiotics and combinations thereof.

Also, the novel method of preparing the drug delivery system according to the invention enables incorporation of aggregated drug particles into the pseudoplastic gel to obtain a slow release action. Thus, it is now possible to inject aggregated drugs to a desired site in the human or animal body and, at the same time, give these drugs a biocompatible protection in vivo. The upper limit of the drug particle diameter has been determined to be about 1000 µm and this means that large as well as small drug particles can be aggregated and then incorporated into the gel. Drug substances being very active require a smaller amount than less active ones. Optionally, the small drug particles can be aggregated with several layers, and thereby delay the drug release further, provided the diameter is less than about 1000 µm. Of course, this can be done in a controlled fashion enabling the design of drug delivery systems with one or more drugs having desired release rates. According to the invention it is, thus, possible to incorporate aggregated, for example lactide-aggregated, drugs in the pseudoplastic gel to achieve a depot action of the drug in vivo. The preferred amount of lactide is fron about 25 to about 99 % (w/w). By aggregating the drugs in varying degrees, release rates within desired ranges can be obtained. Thus, it is possible to aggregate the pharmacologically active substances to the same extent to provide a uniformly controlled drug delivery rate. Alternatively, the pharmacologically active substances are aggregated to a different extent to provide

differently controlled drug delivery rates and, thereby, a wider drug delivery range. Also, the drug delivery system may comprise non-aggregated active substance(s) so that drug delivery will start without delay.

As appreciated from the above, water unsoluble as well as water-soluble drugs can be given a slow release rate in vivo by aggregating and incorporating thereof in a pseudoplastic gel according to the method of the invention.

The following Examples are intended to illustrate the invention further without limiting the scope thereof.

Example 1

This example shows typical drug release rates of a drug delivery system according to the present invention. High molecular weight d,ℓ poly lactide was used to encapsulate albumin. The method of preparation was solvent evaporation which, optionally, was performed repeatedly to obtain larger beads of lactid aggregated albumin. Thereafter, the pseudoplastic combination was prepared as described above and the different combinations were injected into test tubes containing physiological saline.

The results are shown in Fig. 1, wherein the ▲ - ▲ curve represents an albumin/lactide ratio of 75/25 w/w%, the ● - ● represents an albumin/lactide ratio of 50/50 w/w%, and the ✱ - ✱ curve represents an albumin/lactide ratio of 25/75 w/w%.

From Fig. 1 it appears that the higher the lactid content the longer duration of the drug delivery. The largest beads, represented by ✱ - ✱ in Fig. 1 are about 200 μm in diameter and have their maximum release after about 7 weeks. The least aggregated particles, represented by ▲ - ▲ in the figure are about 15 μm in diameter and have their maximum release after about 1 to 2 weeks. The intermediate particles, represented by ● - ● in the figure are only illustrative and it should be

understood that any size in between the two outermost curves are obtainable. The 200 μm beads are sprayed twice but it is, of course, possible to repeat the spraying more times provided the size does not exceed about 1000 μm being the upper limit for incorporaion into the drug delivery system according to the invention. Earlier drug release than the 15 μm particles can be obtained by incorporating non aggregated forms of the drug into the combination. In Fig. 1, 100% release equals the maximum obtainable.

Example 2

This example compares the amount of drug powder (tested compounds: albumin mw 60 000 and lysozyme mw 10 000) aspirated into saline and pseudoplastic gel, respectively.

Drug powder of the tested compounds was put into a syringe from a glass injection vial by injecting a fixed amount of fluid (ie gel or saline) and aspirating the fluid-powder mixture once through a 20 gauge injection needle. The aspirated amount of powder was measured. The results are given in Table 1 below.

Table 1

Powder	% powder aspirated into	
	saline	pseudoplastic gel
Albumin	80	90
Albumin, lactide aggr.	20	95
Lysozyme	75	95
Lysozyme, lactide aggr.	25	95

Most of the losses using saline as the aspirating fluid was due to aggregation in the mixing vial. By allowing over night mixing of the powder and the test fluid the recovery of the albumin and lysozyme was almost 100% whereas the recovery of the lactide bead preparations did not change.

Accordingly, the present invention allows preparation and injection of water unsoluble and badly soluble drugs in a

substantially more rapid and economical way compared to prior art. Furthermore, it allows injection of biocompatible depot preparations having controlled drug delivery rates.

Medical applications possible to perform in view of the basic teachings of the present invention are obvious for a person skilled in the art. As an example, there can be mentioned combination preparations of, for example, streptokinase and heparin aggregated suitably and incorporated in a pseudoplastic gel for administration in the vicinity of the coronary vessels to prevent coronary embolism.

CLAIMS

1. A drug delivery system comprising one or more pharmacologically active substances and a polysaccharide matrix having pseudoplastic properties, wherein the active substances are aggregated to provide a slow release or depot action thereof, wherein the drug delivery system is injectable into a desired site in the human or animal body, and wherein the drug delivery system is biocompatible.

2. A drug delivery system according to claim 1, wherein the pharmacologically active substances are aggregated with d,ℓ polylactide.

3. A drug delivery system according to claims 1 or 2, wherein the pharmacologically active substances are aggregated with 25-99% (w/w) d,ℓ polylactide.

4. A drug delivery system according to claims 1-3, wherein the maximum diameter of the aggregated substances is about 1000 μm.

5. A drug delivery system according to claims 1-4, wherein the pharmacologically active substances are aggregated to the same extent to provide a uniformly controlled drug delivery rate.

6. A drug delivery system according to claims 1-4, wherein the pharmacologically active substances are aggregated to a different extent to provide differently controlled drug delivery rates and, thereby, a wider drug delivery range.

7. A drug delivery system according to claim 6, wherein it also comprises non-aggregated active substance(s) so that drug delivery will start without delay.

8. A drug delivery sytem according to claims 1-7, wherein the matrix comprises 0,05 to 20 % (w/w) of the total system.

9. A drug delivery system according to claims 1-8, wherein the polysaccharide matrix is selected from the group consisting of glucose aminoglucans, hydroxy ethyl cellulose, carboxy methyl cellulose, and xanthan gum.

10. A drug delivery system according to claims 1-9, wherein the pharmacologically active substances are selected from the group consisting of hormones, growth factors, enzyemes, antibiotics and combinations thereof.

11. A drug delivery system according to claims 1-10, wherein the pharmacologically active substances are water unsoluble, semi soluble, or water soluble.

12. A method of parental injection of water unsoluble or semi soluble drugs, wherein one ore more pharmacologically active substances are brought together with a pseudoplastic gel in a vial, the combination is aspirated into a syringe provided with a cannula, the aspirating procedure being repeated, under visual observation, until substantially all of the active substances are incorporated into the pseudoplastic gel.

13. A method according to claim 12, wherein the active substances are aggregated by solvent evaporation prior to combining with the pseudoplastic gel.

14. A method according to claim 13, wherein the aggegation is performed with d,ℓ-poly lactide.

15. A method according to claim 14, wherein the aggegation is performed with 25-99% w/w d,ℓ-poly lactide.

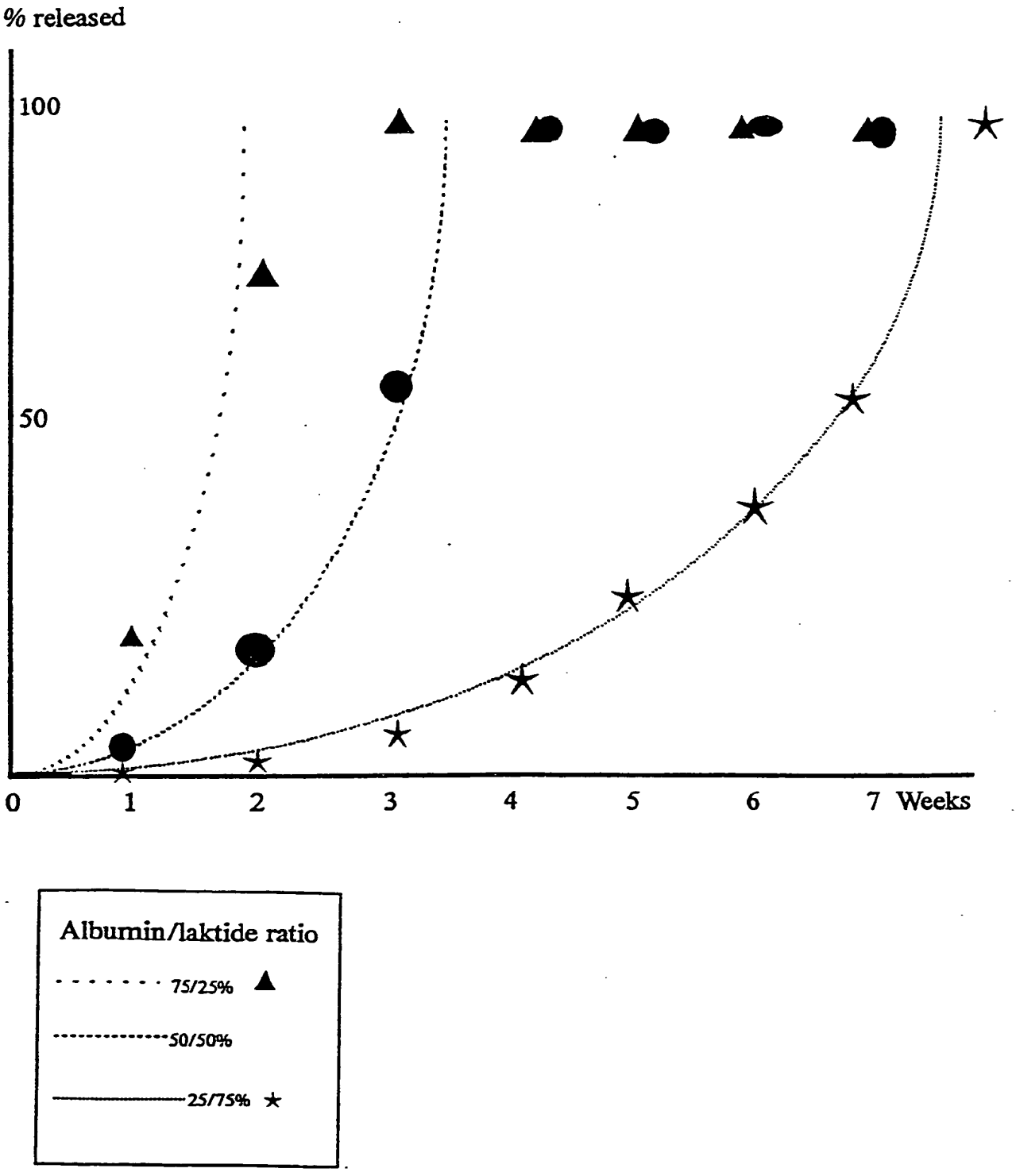
16. A method according to claims 13-15, wherein the aggregation step is repeated to provide slower drug delivery rates.

17. A method according to claims 13-16, wherein the aggregation step is performed in varying degrees to provide differently

controlled drug delivery rates and, thereby, a wider drug delivery range.

18. The use of a drug delivery system according to claims 1-11 for providing slow release of the active substance(s) in a biocompatible environment following in vivo injection thereof.

FIGURE 1


% released
100
50
0
1
2
3
4
5
6
7 Weeks
Albumin/laktide ratio
75/25%
50/50%
25/75%

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00683

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 9/00, 9/22, 47/36, 47/38

II. FIELDS SEARCHED

Minimum Documentation Searched[7]	
Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	Dialog Information Service, File 351 WPI, WPI Acc No 88-116590/17 & JP, A, 63063624 (KAKIZAKI) 22 March 1988, abstract --	1-11
Y	US, A, 4474752 (JOHN L. HASLAM ET AL.) 2 October 1984, see column 2, line 40 - line 55; column 4, line 15 - line 20 --	1-11
Y	EP, A3, 0140255 (SUMITOMO CHEMICAL COMPANY, LIMITED) 8 May 1985, see page 2 - page 7 --	1-11
Y	EP, A2, 0224987 (BIOMATRIX, INC.) 10 June 1987, see page 6, line 5 - page 10, line 35 --	1-11

* Special categories of cited documents: [10]

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25th January 1991	1991 -01- 28
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Niklas Forslund

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	DE, A1, 3626868 (BAYER AG) 11 February 1988, see the whole document --	1-11
A	EP, A2, 0221505 (SCLAVO S.P.A.) 13 May 1987, see the whole document --	1-11

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 12-17, because they relate to subject matter not required to be searched by this Authority, namely:

Method of treating the human or animal body according to PCT-rule 39.1 (IV)

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 90/00683

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 90-12-28
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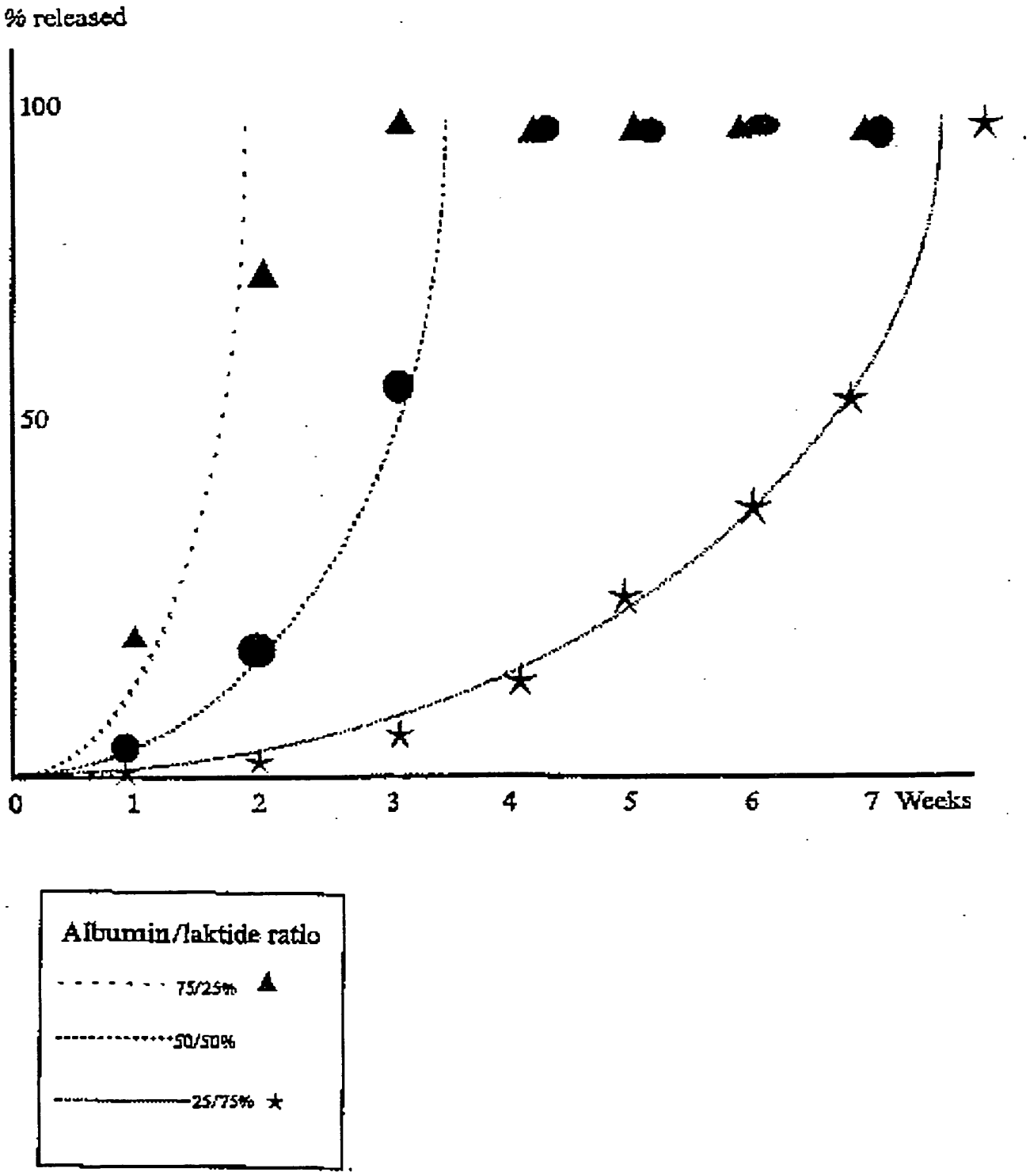
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4474752	84-10-02	CA-A-	1224148	87-07-14
		EP-A-	0126684	84-11-28
EP-A3- 0140255	85-05-08	EP-A-	0138216	85-04-24
		EP-A-	0139286	85-05-02
		JP-A-	60084213	85-05-13
		US-A-	4774091	88-09-27
		US-A-	4855134	89-08-08
		JP-A-	60089418	85-05-20
		JP-A-	60097918	85-05-31
		JP-A-	60112713	85-06-19
EP-A2- 0224987	87-06-10	AU-B-	595524	90-04-05
		AU-D-	6090386	87-06-04
		JP-A-	62129226	87-06-11
DE-A1- 3626868	88-02-11	EP-A-	0257320	88-03-02
		JP-A-	63044517	88-02-25
EP-A2- 0221505	87-05-13	AU-D-	6427886	87-05-14
		JP-A-	62114919	87-05-26

FIGURE 1


% released
100
50
0
1
2
3
4
5
6
7 Weeks
Albumin/laktide ratio
75/25%
50/50%
25/75%